CLAIM + DETAILED DESCRIPTION

[Claim(s)]
[Claim 1]A sustained-release medicinal composition containing an enteric polymer, an acid solubility polymer, and a medicine.
[Claim 2]The sustained-release medicinal composition according to claim 1 whose enteric polymer is a methacrylic-acid-methyl-methacrylate copolymer and whose acid solubility polymer is methacrylic-acid methyl-methacrylic-acid butyl-methacrylic-acid dimethylamino ECHIRUKO polymer or polyvinyl acetal diethyl acetate.
[Claim 3]The sustained-release medicinal composition according to claim 1 or 2 whose content of an acid solubility polymer content of an enteric polymer is 5 to 15.3 weight % among a medicinal composition, and is 0.8 to 5 weight % among a medicinal composition.
[Claim 4]A sustained-release medicinal composition of Claims 1-3 which coat medicine content nucleus granulation with an enteric polymer and an acid solubility polymer one by one given in any 1 paragraph.
[Claim 5]A claim which is sustained-release granular preparation - a sustained-release medicinal composition of four given in any 1 paragraph.
[Claim 6]A sustained-release medicinal composition containing sustained-release granulation according to claim 5 and quick-acting granulation.
[Claim 7]The sustained-release medicinal composition according to claim 6 whose medicine weight ratios of sustained-release granulation according to claim 5 and quick-acting granulation are 1:1-20:1.
[Claim 8]Sustained-release granular preparation which carried out stacked volume of the immediate-release medicine layer to the sustained-release granulation according to claim 5 at a rate of 1:1-20:1 by a medicine weight ratio.
[Claim 9]A sustained-release medicinal composition of Claims 5-8 which are a kind as which a medicine is chosen from a basic drug and/or its salt permitted physiologically, or two sorts or more given in any 1 paragraph.
[Claim 10]The sustained-release granular preparation according to claim 9 whose basic drugs are nicardipine and/or its salt permitted physiologically.

[Detailed Description of the Invention]
[0001]
[Field of the Invention]Especially this invention relates to a sustained-release medicinal composition suitable as sustained-release granular preparation by which drug release was arbitrarily controlled in the gastric pH field and the enteral pH range about a sustained-release medicinal composition.
[0002]
[Description of the Prior Art]Sustained release preparations decrease the number of times of administration of a tablet, and raise a patient's compliance, and heightening a curative effect etc. has many advantages on Medical Science Division.

[0003]In order to heighten the curative effect by sustained release preparations, The what is called zero-order discharge type sustained release preparations which need to maintain effective blood drug concentration over a long time, and are not concerned with the solubility of the medicine to water, acidity, basicity, etc. as sustained release preparations, but emit a fixed quantity of medicines per unit time under various physiological environment after internal use are demanded. In the sustained release preparations which contain an unstable medicine, the medicine which has the character to receive a first-pass effect, etc. at a tunica-mucosa-ventriculi stimulativeness medicine and acidic environment, it is anxious for controlling the drug release within the stomach and carrying out controlled release of the medicine henceforth [small intestine].
[0004]Therefore, in order to obtain sustained release preparations conventionally, the trial of the various discharge controlling methods is made, and the spread type discharge controlling method and the eluted type discharge controlling method are known as the typical thing.
[0005]There are a matrix type GURADEYUMETTO form which distributed the medicine in the coat type fine dialysis membrane pellet which covered the medicine content nucleus with the water-insoluble sex skin film, and the fine dialysis membrane capsule and a water-insoluble nature base, and a wax-matrix form in the spread type discharge controlling method.
[0006]There are the coat type Sepang Sour type which covered the medicine content nucleus with the water-soluble coat, MATORIKUSSU type spa stub type which distributed the medicine in the water-soluble base, span tab type, and a RONTABU form in the eluted type discharge controlling method. There is also the procedure of controlling drug release by alimentary canal pH in the eluted type discharge controlling method, using an enteric base as a water-soluble base. (Development Vol.13 "medicine sending method" Hirokawa Publishing of a drug)
[0007]The sustained release preparations which covered with the water-insoluble sex skin film the nucleus which distributed the medicine in the enteric base (JP,S64-7047,B), The sustained release preparations which covered the medicine content nucleus with the water-insoluble sex skin film, and covered the enteric coat further (JP,H6-21066,B), The discharge controlling method which combined spread types, such as sustained release preparations (JP,H4-234812,A) which covered the medicine content nucleus with the coat which consists of an enteric base and a water-insoluble nature base, and an eluted type is also proposed.
[0008]The following things are mentioned as a problem when the sustained release preparations by these conventional discharge controlling methods are administered orally.
[0009](1) Although it is said by the drug release controlling method by a water-insoluble sex skin film that zero-order discharge is easy to be acquired, When the solubility of a medicine shows pH dependency, there is a possibility that drug release after that drug release speed changes with change (about pH1-pH8) of alimentary canal pH and a small intestine cannot control the drug release within the stomach in a desirable medicine.
[0010](2) By the drug release controlling method by a water-soluble coat, zero-order discharge is hard to be acquired and there is a possibility that drug release after a small intestine cannot control the drug release within the stomach in a desirable medicine. In the drug release controlling method using an enteric base, although it is able for the drug release after a small intestine to control the drug release within the stomach in a desirable

medicine, and to send a medicine into a small intestine, drug release has a possibility that it may not be controlled by zero-order discharge.
[0011](3) By the matrix type discharge controlling method by the water-insoluble nature base and a water-soluble base, drug release speed shows a downward tendency with progress of time, and zero-order discharge is difficult to get. There is a possibility of causing a burst phenomenon in an alimentary canal.
[0012](4) In the stomach, control drug release, send a medicine into a small intestine, and it is considered as the drug release controlling method which made it possible to carry out zero-order discharge of the drug release, The drug release controlling method which covered with the water-insoluble sex skin film the nucleus which distributed the medicine in the enteric base, the drug release controlling method which covered the medicine content nucleus with the water-insoluble sex skin film, and covered the enteric coat further, and the drug release controlling method which covered the medicine content nucleus with the coat which consists of an enteric base and a water-insoluble nature base are proposed. However, there is a possibility that drug release speed may change with change (pH 5-8) of pH in a small intestine within a small intestine in response to influence also in these drug release controlling methods in the solubility of an enteric base. When the solubility of a medicine shows pH dependency, it is guessed that it will become still more difficult to carry out controlled release of the medicine.
[0013]When these things actually medicate a patient with a tablet, and the releasing speed of a medicine changes between individuals and within an individual with the physiological factor of an alimentary canal especially the fluidity of digestive juices, quantity or the quality of a meal, and quantity, change drug levels in the blood. That is, changing bioavailability is shown, continuation-ization of drug effect is attained in all the patients, and it has become a cause which cannot be declared that the suitable curative effect is acquired. That is, the sustained-release medicinal composition by which drug release was arbitrarily controlled in the gastric pH field and the enteral pH range has not been obtained yet at present.
[0014]
[Problem to be solved by the invention]Therefore, an object of this invention is to provide the medicinal composition which can control drug release arbitrarily.
[0015]
[Means for solving problem]In [as a result of this invention persons' repeating research wholeheartedly about the more practical drug release controlling method in such the actual condition using various bases for a tablet] the above-mentioned conventional sustained release preparations, In order to aim at stabilization of drug-levels-in-the-blood transition, continuation-izing of drug effect, and improvement in a curative effect, By covering a medicine content nucleus with an enteric coat, and also covering with an acid solubility coat paying attention to it being effective to adjust the drug release under various pH environments freely, and to carry out controlled release arbitrarily, it found out that the outstanding drug release control effect was acquired, and this invention was completed.
[0016]That is, a sustained-release medicinal composition, wherein this invention contains an enteric polymer, an acid solubility polymer, and a medicine is provided.
[0017]
[Mode for carrying out the invention]As for pH of an alimentary canal, it is known

henceforth [the pH six to 7 neighborhood and a time cecum] for that it is [which it is / which is the pH one to 3.5 neighborhood in the stomach / the pH five to 6 neighborhood in the duodenum] the pH 8 neighborhood in jejunum. Generally especially in drug absorption nature, it is known with pH 6.5 and pH 7.2 participating in drug release nature from a tablet as pH 1.2 and enteral pH as gastric pH. The sustained-release medicinal composition of this invention can control arbitrarily drug release in both pH in which a gastric pH field (pH 1.2) and an enteral pH range especially pH 6.5, and pH 7.2 carried out the neighborhood.

[0018]As an enteric base used by this invention, hydroxypropylmethylcellulose phthalate (a brand name: HP-55, HP-50, the Shin-etsu chemicals company make), A methacrylic-acid-methyl-methacrylate copolymer (a brand name: OIDORAGITTO L100 and OIDORAGITTO L100-55, OIDORAGITTO S100, product made by **-**********), A methacrylic acid-ethyl acrylate copolymer (a brand name: OIDORAGITTO L30D-55, product made by **-**********), Hydroxypropyl methylcellulose acetate succinate (a brand name: AQOAT, the Shin-etsu chemicals company make), carboxy methyl ethyl cellulose (a brand name: CMEC, Freund Industrial make), etc. mention, and it is ****. These can also use a kind independently and can also use it combining two or more sorts. a thing desirable [among these] -- a methacrylic-acid-methyl-methacrylate copolymer (brand name: -- OIDORAGITTO L100 (synonym: the methacrylic-acid copolymer L).) They are OIDORAGITTO L100-55 (synonym: the methacrylic-acid copolymer L), OIDORAGITTO S100 (synonym: the methacrylic-acid copolymer S), products made by **-**********, or these mixtures.

[0019]Although desirable content of an enteric polymer in a constituent of this invention changes with application purposes, such as a medicine, a released type, and a releasing speed, its 1 to 30 weight % is preferred, especially its 3 to 20 weight % is preferred, and its 5 to 15.3 weight % is still more preferred.

[0020]As an acid solubility polymer used by this invention, it is a polymer used for a medicinal composition for the purpose, such as covering, and what is necessary is just meltable and it is not limited in particular to acid. As such a polymer, the amino alkyl methacrylate copolymer E (a brand name: OIDORAGITTO E100, product made by **-**********), polyvinyl acetal diethyl acetate (a brand name: AEA, Sankyo Co., Ltd. make), etc. are mentioned, for example. A kind may be independently used for these and may be used for them combining two or more sorts.

[0021]Although content of an acid solubility polymer in a constituent of this invention changes with dosage form designs, such as a medicine, a released type, and a releasing speed, its 0.1 to 10 weight % is preferred, especially its 0.5 to 8 weight % is preferred, and its 0.8 to 5 weight % is still more preferred.

[0022]A medicine used by this invention will not be restricted especially if drug effect is expected by internal use. Namely, agents for circulation organs, such as a center and agents for peripheral nerves, such as bends diazepine, nifedipine, and nicardipine, An agent for respiratory organs, an agent for digestive organs, a hormone drug, a vitamin tablet, an agent for allergy, Agents for painkilling, such as an agent for alleviation of fever, ketoprofen, and ketotifen, cisplatin, Agents for tumors, such as ADOREA mycin and 5-fluorouracil, fosfomycin, It can be chosen from fields, such as chemotherapeutic drugs, such as antibiotic preparations, such as methicillin, bifonazole, and miconazole, and cannot be concerned with the solubility of a medicine to water, acidity, basicity, etc.,

but a medicine usually used can be blended. Salt with which these medicines are permitted physiologically can also be used. As a medicine suitably used in this invention, a basic drug in which the solubility of pH dependency is shown is mentioned. Although the solubility of nicardipine hydrochloride of a medicine is remarkably [to a gastric pH field] low in a pH range in a small intestine, [in a basic drug] Since to control drug release within the stomach, to make a medicine send a small intestine in a high content, and to carry out drug release at fixed speed in the small intestine whole region, since it has the character to receive a first-pass effect in liver is desired, it is especially desirable.
[0023]Although the content of the medicine in the constituent of this invention changes with the kind of the medicine, and purposes of a dosage form design, its 0.1 to 40 weight % is preferred, its 0.5 to 30 weight % is more preferred, and its 1 to 200 weight % is still more preferred.
[0024]The combination procedure of the enteric polymer in the medicinal composition of this invention, an acid solubility polymer, and a medicine should just be a procedure used by manufacture of the medicinal composition, and is not usually limited in particular. For example, what is necessary is to mix and carry out granulation of these ingredients and optional components, or to create the nucleus containing a medicine, and just to make this cover an enteric polymer and an acid solubility polymer. The most desirable procedure in these is the procedure of creating the granulation of the nucleus containing a medicine, coating this with the solution containing an enteric polymer, and coating with the solution which contains an acid solubility polymer in after an appropriate time.
[0025]As for the sustained-release medicinal composition of this invention, it is preferred to consider it as granular preparation, and the granulation used as the intermediate product of this granulation and a medicinal composition can be prepared using the usual tablet art of a description or its strange method, and the improving method to the Pharmacopoeia of Japan etc. As such a procedure, medicine content nucleus granulation is prepared by dry granulation, an agitation granulation method, fluidized bed granulation method, melt-cooling-granulation method, extrusion granulation method, a coating granulation method, etc., for example. The tablet materials used on the occasion of preparation of medicine content nucleus granulation are an excipient, a binder, a lubricant, condensation inhibitor, an inactive nuclear particle, an organic acid, a surface-active agent, etc., and if usually used for a medicinal composition, they can use all.
[0026]Medicine content nucleus granulation which is an intermediate product has that preferred whose mean particle size is 100-1200 micrometers, and especially its thing that is 100-500 micrometers is preferred. Medicine content nucleus granulation in which immediate-release drug release is shown in this invention is used suitably. Although medicine content in prepared medicine content nucleus granulation is 1 to 50 weight % preferably, it is not necessarily limited to this quantity, but can be changed with a physicochemical quality of a medicine, dosage, etc.
[0027]The pan coating method, a fluid bed coating method, a rolling fluid bed coating method, etc. can be used for a procedure of covering medicine content nucleus granulation with an enteric polymer. this -- medicine content nucleus granulation -- rolling -- and -- or coating fluid dissolved or suspended in a solvent in an enteric polymer is sprayed on a layer made to flow, a solvent is dried by warm air, and an enteric coat is made to form in an outer layer of medicine content nucleus granulation
[0028]It is operated like a time of covering an enteric coat using an acid solubility

polymer, and an acid solubility film layer is made to form in an outer layer of an enteric film layer.
[0029]When covering an enteric polymer, or when covering an acid solubility polymer, plasticizers, a lubricant, a pigment, correctives, etc. are blended, but if these are usually used, they can use all. As a solvent, methanol, ethanol, isopropanol, chloroform, acetone, methylene chloride, water, etc. are mentioned. These may be used alone, and they may be used, mixing suitably.
[0030]Thus, desirable mean particle diameter of prepared sustained-release granular preparation is 100-2000 micrometers, and especially its 100-500 micrometers are preferred.
[0031]Since granulation obtained in this way has a fixed emission characteristic, it can be used as a sustained-release medicine excellent only in this granulation. This granulation can be used in combination with usual quick-acting granulation, the conventional sustained-release granulation, etc. which have not been covered with a polymer. Among these, a certain amount of burst size is required of zero-order, for example, combination with quick-acting granulation is effective in medicine for poorly soluble circulatory organs, such as nifedipine and nicardipine.
[0032]About combination with a quick-acting drug composition, what obtained it into it by carrying out stacked volume of the immediate-release medicine layer to sustained-release granulation of this invention can be illustrated. This will be easily obtained, if a quick-acting drug composition, i.e., a constituent which consists of an optional component on tablets other than a medicine and a polymer for coating, is coated on a medicinal composition of this invention.
[0033]In combination of the above, and a medicinal composition of this invention and a quick-acting medicine, a medicinal composition and the conventional sustained-release drug composition of this invention A gradual release part, What is necessary is just to adjust suitably a rate of a gradual release part and a fast-discharging part, in order to acquire moderate first stage blood drug concentration and its prolonged effect if a quick-acting constituent which consists of an optional component on a medicine without a coated polymer and tablets other than a polymer for coating is used as a fast-discharging part. It is preferred to be a weight ratio and to set an amount of the drug in an amount of the drug in sustained-release granulation, quick-acting granulation, or an immediate release layer to 1:2-50:1 generally, 2:3-especially 30:1 are preferred, and 1:1-20:1 are still more preferred.
[0034]Nicardipine and/or those salt permitted physiologically are used for the best thing in an embodiment of the invention as a medicine, This is coated with granular sucrose, it is considered as medicine content nucleus granulation, a methacrylic-acid copolymer coat is created to this, and the coat of amino alkyl methacrylate is made to generate on this coat after an appropriate time.
[0035]
[Working example]Although an embodiment is shown below and this invention is explained to it in more detail, these do not limit this invention at all. Unless it mentions specially, % shows weight %.
[0036]comparative example 1 purified-sucrose spherical granulation (brand name: -- Nonpareil 103 -- 24 - 32 meshes) To the Freund Industrial make 200g, 70 g of nicardipine hydrochloride, 70 g of hydroxypropyl methyl sirloins (brand name: TC-5, the

Shin-etsu chemicals company make), 32 g of polysorbate 80 (brand name: TO-10 M, made in Nikko Chemicals), It dried, after coating with the coating fluid which dissolved and distributed the talc 40g (brand name: victory light SK-C, the Katsumitsu mountain mining station company make) and the water 178g at 1610 g of ethanol with a rolling fluid bed coating method, and drug-containing granules were obtained.

[0037]the granulation 100g obtained by the comparative example 2 comparative example 1 -- 50g (brand name: -- ethocell N-10-G.) of ethyl cellulose It dries, after coating with the coating fluid 100g which dissolved and distributed the Shin-etsu chemicals company make, 5 g of triethyl citrate (brand name: Citroflex, the Chugai trade company make), and the talc 15g at 930 g of ethanol with a rolling fluid bed coating method, and it is sustained-release granulation ****.

[0038]Product sucrose made from comparative example trispermy spherical granulation To 200 g, 70 g of nicardipine hydrochloride, 70 g of ethyl cellulose, Polysorbate 80 It dried, after coating with coating fluid which dissolved and distributed 32 g and the talc 40g at 1788 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0039]Into the granulation 100g obtained by the comparative example 4 comparative example 1, the methacrylic-acid copolymer L(a brand name: OIDORAGITTO L100, product made by **-**********) 70g, It dried, after coating with the coating fluid 120g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0040]Into the comparative example 5 purified-sucrose spherical granulation 200g, 70 g of nicardipine hydrochloride, the methacrylic-acid copolymer L70g, Polysorbate 80 It dried, after coating with coating fluid which dissolved and distributed 32 g and the talc 40g at 1788 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0041]It dried, after coating with the coating fluid 60g which dissolved and distributed 50 g of ethyl cellulose, 5 g of triethyl citrate, and the talc 15g at 930 g of ethanol with a rolling fluid bed coating method into the granulation 100g obtained by the comparative example 6 comparative example 5, and sustained-release granulation was obtained.

[0042]Into the granulation 100g obtained by the comparative example 7 comparative example 1, 50 g of ethyl cellulose, 5 g of triethyl citrate, It dries, after coating with the coating fluid 60g which dissolved and distributed the talc 15g at 930 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 110g which dissolved and distributed the methacrylic acid copolymer L70g, 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0043]Into the granulation 100g obtained by the comparative example 8 comparative example 1, the methacrylic-acid copolymer L30g, It dried, after coating with the coating fluid 120g which dissolved and distributed 30 g of ethylcellulose, 6 g of triethyl citrate, the talc 10g, and the water 50g at 874 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0044]Granulation obtained by the comparative example 9 comparative example 6 and granulation obtained by the comparative example 1 were mixed so that it might be set to 3:1 in the amount of nicardipine hydrochloride, and sustained-release granulation was

obtained.

[0045]Into the embodiment 1(1) purified-sucrose spherical granulation 200g, 70 g of nicardipine hydrochloride, The hydroxypropyl methylcellulose 70g, polysorbate 80 It dried, after coating with coating fluid which dissolved and distributed 32 g, the talc 40g, and the water 178g at 1610 g of ethanol with a rolling fluid bed coating method, and drug-containing granules were obtained.

Into the obtained granulation 100g, above (2) The methacrylic-acid copolymer S(a brand name: OIDORAGITTO S100, product made by **-**********) 70g, It dries, after coating with the coating fluid 78g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0046]Into the granulation 100g obtained in embodiment 2 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 78g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0047]Into the granulation 100g obtained in embodiment 3 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 240g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0048]Into the granulation 100g obtained in embodiment 4 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 240g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0049]Into the granulation 100g obtained in embodiment 5 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 240g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 40g which dissolved and distributed 12 g of polyvinyl acetal diethyl acetate (a brand name: AEA, Sankyo make), the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained. When coating polyvinyl acetal diethyl acetate, certain quantity addition of the macrogol 6000 can be carried out as occasion demands at coating fluid.

[0050]Into the granulation 100g obtained in embodiment 6 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 30g which

dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 10g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0051]Into the granulation 100g obtained in embodiment 7 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 30g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 330g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0052]Into the granulation 100g obtained in embodiment 8 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 400g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 10g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0053]Into the granulation 100g obtained in embodiment 9 Embodiment 1 (1), the methacrylic-acid copolymer S70g, It dries, after coating with the coating fluid 400g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 330g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0054]Into the granulation 100g obtained in embodiment 10 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic acid copolymer L46.7g, 7 g of triethyl citrate, It dries, after coating with the coating fluid 78g which dissolved and distributed the talc 7g and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0055]Into the granulation 100g obtained in embodiment 11 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic acid copolymer L46.7g, 7 g of triethyl citrate, It dries, after coating with the coating fluid 78g which dissolved and distributed the talc 7g and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0056]Into the granulation 100g obtained in embodiment 12 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic acid copolymer L46.7g, 7 g of triethyl citrate, It dries, after coating with the coating fluid 240g which dissolved and distributed the talc 7g and the water 100g at 916 g of ethanol with a rolling fluid bed

coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0057]Into the granulation 100g obtained in embodiment 13 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic acid copolymer L46.7g, 7 g of triethyl citrate, It dries, after coating with the coating fluid 240g which dissolved and distributed the talc 7g and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0058]Into the granulation 100g obtained in embodiment 14 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic-acid copolymer L46.7g, 7 g of triethyl citrate, It dries, after coating with the coating fluid 160g which dissolved and distributed the talc 7g and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 65g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0059]Into the granulation 100g obtained in embodiment 15 Embodiment 1 (1), the methacrylic-acid copolymer S23.3g, The methacrylic-acid copolymer L46.7g, 7 g of triethyl citrate, the talc 7g, It dries, after coating with the coating fluid 160g which dissolved and distributed the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 100g which dissolved and distributed 12 g of polyvinyl acetal diethyl acetate (a brand name: AEA, Sankyo Co., Ltd. make), the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained. When coating polyvinyl acetal diethyl acetate, certain quantity addition of the macrogol 6000 can be carried out as occasion demands at coating fluid.

[0060]Into the granulation 100g obtained in embodiment 16 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 78g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0061]Into the granulation 100g obtained in embodiment 17 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 78g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.

[0062]Into the granulation 100g obtained in embodiment 18 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 240g

which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 25g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.
[0063]Into the granulation 100g obtained in embodiment 19 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 240g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 165g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.
[0064]Into the granulation 100g obtained in embodiment 20 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 125g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 65g which dissolved and distributed the amino alkyl methacrylate copolymer E12g, the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.
[0065]Into the granulation 100g obtained in embodiment 21 Embodiment 1 (1), the methacrylic-acid copolymer L70g, It dries, after coating with the coating fluid 125g which dissolved and distributed 7 g of triethyl citrate, the talc 7g, and the water 100g at 916 g of ethanol with a rolling fluid bed coating method, It dried, after coating with the coating fluid 100g which dissolved and distributed 12 g of polyvinyl acetal diethyl acetate (a brand name: AEA, Sankyo Co., Ltd. make), the talc 6g, and the water 18g at 364 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained. When coating polyvinyl acetal diethyl acetate, certain quantity addition of the macrogol 6000 can be carried out as occasion demands at coating fluid.
[0066]The granulation obtained in embodiment 22 Embodiment 1 (1) and the granulation obtained in Embodiment 14 were mixed so that it might be set to 3:1 in the amount of nicardipine hydrochloride, and sustained-release granulation was obtained.
[0067]Into the granulation 100g obtained in embodiment 23 Embodiment 14, 70 g of nicardipine hydrochloride, The hydroxypropyl methylcellulose 70g, polysorbate 80 It dried, after coating with the coating fluid 156g which dissolved and distributed 32 g, the talc 40g, and the water 178g at 1610 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.
[0068]The granulation obtained in embodiment 24 Embodiment 1 (1) and the granulation obtained in Embodiment 15 were mixed so that it might be set to 3:1 in the amount of nicardipine hydrochloride, and sustained-release granulation was obtained.
[0069]Into the granulation 100g obtained in embodiment 25 Embodiment 15, 70 g of nicardipine hydrochloride, The hydroxypropyl methylcellulose 70g, polysorbate 80 It dried, after coating with the coating fluid 155g which dissolved and distributed 32 g, the talc 40g, and the water 178g at 1610 g of ethanol with a rolling fluid bed coating method, and sustained-release granulation was obtained.
[0070](Example of an examination) The kinetics in medicine blood when administered orally to the discharge nature and the dog of a medicine (nicardipine hydrochloride) was

compared as follows about the sustained-release granulation obtained by the sustained-release granulation and the comparative example of this invention which were acquired in the embodiment.

[0071]The example 1 (elution test) of an examination

40 mg of nicardipine hydrochloride considerable quantity of sustained-release granulation obtained by embodiment and a comparative example is used, and it is the Pharmacopoeia of Japan. General Test Procedures A dissolution test A releasing speed of a medicine was measured by the 2nd method (paddle method). Test solution was 900 ml in volume using the official 1st liquid (pH 1.2), pH 6.5 phosphate buffer solution (polysorbate 80 0.1% content), and pH 7.2 phosphate buffer solution (polysorbate 80 0.1% content). Preset temperature was 37 **, paddle number of rotations was 100 rpm, and a quantum of nicardipine hydrochloride eluted to test solution was measured with an extinction method (wavelength of 355 nm).

[0072](Test result) A test result concerning sustained-release granulation of Embodiments 1-25 to drawing 1 - 9 in a test result about sustained-release granulation of the comparative examples 1-9 is shown in drawing 10 - 34. a kind (the methacrylic-acid copolymer L.) of enteric polymer which uses sustained-release granulation of this invention for an enteric coat from this result a kind (the amino alkyl methacrylate copolymer E.) of acid solubility polymer used for the methacrylic-acid copolymers S or these mixtures, quantity (it is about 5 to 15 weight % to medicine content nucleus granulation), and an acid solubility coat [by changing polyvinyl acetal diethyl acetate and quantity (it is about 0.8 to 5 weight % to medicine content nucleus granulation)] In a gastric pH field (pH 1.2) and an enteral pH range (pH 6.5, pH 7.2), it is clear that it is arbitrarily controlable over a long time in drug release. That is, a gradual release tablet of this invention is arbitrarily controlable over a long time.

[0073]Drug release is controlled in a gastric pH field (pH 1.2) which nicardipine hydrochloride is expected in sustained-release granulation of an embodiment which shows various drug release patterns, Sustained-release granulation in which the same drug release speed is shown in an enteral pH range (pH 6.5, pH 7.2) is a thing of Embodiment 14, Embodiment 15 and Embodiment 22 combined with these and a fast-discharging part, Embodiment 23, Embodiment 24, and Embodiment 25.

[0074]The example 2 (kinetics examination in dog medicine blood) of an examination

40 mg of nicardipine hydrochloride considerable quantity of sustained-release granulation obtained by sustained-release granulation and the comparative example 9 which were acquired in Embodiment 22 is administered orally to six male beagles (about 10 kg) made to abstain from food for 12 hours, respectively, It collected blood temporally after medication and asked for blood Nakashio acid nicardipine concentration by a high speed liquid chromatography method.

[0075](Test result) A test result is shown in drawing 35. Sustained-release granulation of this invention showed drug-levels-in-the-blood transition stable over a long time, and also its change of drug levels in the blood between individuals was smaller than this result, and it was clear to have sustained-release [outstanding].

[0076]As an embodiment, an example of an examination, etc. showed, [sustained-release granulation of this invention] It is not concerned with solubility (water, pH) over water of a medicine, but drug release A gastric pH field (pH 1.2) and an enteral pH range, it is possible to control drug release arbitrarily over a long time in both pH in which

especially pH 6.5 and pH 7.2 carried out the neighborhood -- between (inner) stabilization of drug-levels-in-the-blood transition, and an individual -- drug levels in the blood -- strange It is clear that reduction in ** is achieved. By these things, improvement in a curative effect by continuation-izing where drug effect was stabilized, an improvement of a patient's QOL, etc. are expectable in sustained-release granulation of this invention.

[0077]

[Effect of the Invention]According to this invention, the medicinal composition which can control drug release arbitrarily can be provided.